

ORIGINAL ARTICLE

Consanguinity and Risk of Congenital Heart Defects in Bangladesh

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Abstract

Background: Consanguineous marriage have been associated with an increased risk to various forms of inherited disease. Potential role of consanguinity in certain common birth defects is less clear especially with congenital heart defects (CHDs).

Objective: This study was conducted to evaluate the potential role of consanguinity as a risk factor for congenital heart defects (CHDs) in Bangladesh.

Methodology: It was a case control study, conducted from July 2018 to July 2019 at Dhaka Shishu (Children) Hospital. Parents of the children with CHD visited the outpatient department was considered as case. Control was taken from parents of the children who didn't have congenital heart disease. Informed written consent was taken from parents. Data were collected by using a structured questionnaire containing all the variables of interest and analyzed by using SPSS version 21. Chi square test (S^2), Odds ratio (OR) and 95% confidence intervals (CIs) were calculated to estimate the associations between parental consanguinity and all CHDs. Risk factors on bivariate analysis were introduced into a logistic regression model as independent factors and dependent variable was CHDs to find out the association between CHDs and consanguinity.

Results: Among study population consanguinity was present in 33(6.11%) cases. In the case group 23 children (8.85%) were born to consanguineous parents and in control group 10 children (3.57%) were born to consanguineous parents. CHDs were found significantly higher in children born to consanguineous parents ($p < 0.05$). On logistic regression analysis consanguinity ($p = 0.02$) was independently associated with CHDs. Children who born to consanguineous parents had 2.5 times risk of developing CHDs compared to those who were not born to consanguineous parents.

Conclusions: Parental consanguinity is significantly associated with CHDs.

Keywords: Consanguinity, Congenital Heart Defects.

Introduction

CHDs represent approximately one-third of all congenital anomalies and are the most common group of congenital malformations, affecting almost 1% of live births throughout the world.^{1,2} Although advancement in pediatric cardiology and pediatric cardiac surgery have improved long term outcome and promised better quality of life, the etiology of

most congenital heart defects are still unknown. Several chromosomal anomalies, certain maternal illnesses and prenatal exposures to specific therapeutic drugs are recognized risk factor. It is difficult to establish the role of a single factor because the cause of a defect is believed to be multifactorial in many cases.³ Etiology of congenital heart defects are complex and possibly lies within the interaction

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of environmental exposures and inherited factors.⁴ Although CHDs can occur in the setting of multiple birth defects as part of a syndrome, most are found as isolated defects with no syndromic association.

CHD encompasses a range of structural abnormalities of the heart, and in many cases, the factors that predispose an individual to disease are not well understood. CHD associated with well-known genetic syndromes often has a known genetic basis or a defined Mendelian inheritance pattern. In contrast, many forms of non-syndromic CHD are thought to usually result from the combined effects of a number of factors, presumably both genetic and epigenetic.⁵ Despite this complexity, consanguinity could increase the likelihood of disease, particularly if the disease has a recessive or multifactorial inheritance pattern. Despite the many investigations that have been conducted into the relationship between consanguinity and congenital heart disease, the precise nature and significance of the association remains unclear. However, many of the more common CHDs appear to be genetically heterogeneous, whether diagnosed as isolated anomalies or accompanied by other heart defects.⁶

Consanguineous unions afford the possibility that susceptibility genes identical by descent may be inherited through the relatedness of child-bearing couples, potentially leading to disease depending on the prevalence of consanguineous unions and the genetic contribution to disease. For common birth defects such as CHD, which are thought to have a genetic component, consanguinity may contribute to the risk of disease.⁷ From a medical genetics perspective, all marriages between couples related as second cousins or closer are regarded as consanguineous (derived from the Latin *con sanguineus*; i.e. sharing the same blood), and using this definition, it has been estimated that at least 10.4% of the world population are consanguineous.⁷ Fung et al⁸ found parental consanguinity as a risk factor of CHDs.

Lack of enough information about modifiable risk factors for malformations in fetal heart development has impeded the prevention of CHDs. While the origin of non-syndromic CHD that accounts for most of congenital cardiac abnormalities is still under the veil waiting to be further uncovered. An exploration of the contribution of risk factors that are potentially modifiable is particularly important in the context of the growing health burden of CHD.⁹ This study therefore performed to evaluate consanguinity as risk factors of CHD among Bangladeshi population.

Materials and Methods

This study was conducted from July 2018 to July 2019 at Dhaka Shishu (Children) Hospital. The study population was the parents of children visited to the outpatient department of Dhaka Shishu (Children) Hospital. Parents of the children with congenital heart disease visited the out-patient department of paediatric cardiology of Dhaka Shishu (Children) Hospital was considered as case. Control was taken from parents of the children who didn't have congenital heart disease. Children with associated syndromes or major other systemic disease such as Down's syndrome, having congenital anomalies and parents who refused to get involved in the study or to comply with its requirement were excluded. Data were collected by using a structured questionnaire. To minimize recall bias of exposure by mothers, all cases and controls were recruited when they were <1 year old. Data were processed and analyzed by using computer aided statistical software SPSS (Statistical Package for Social Sciences) Version 21. Chi square test (χ^2), Odds ratio (OR) and 95% confidence intervals (CIs) were calculated to estimate the associations between parental consanguinity and all CHDs. Risk factors on bivariate analysis were introduced into a logistic regression model as independent factors and dependent variable was CHDs to find out the association between CHDs and consanguinity.

Results

Parents of 260 children having CHD was enrolled as case and parents of 280 children having no heart disease was taken as control. Consanguinity was present in 33(6.11%) cases. In the case group, 23 children (8.85%) were born to consanguineous parents. In the control group, only 10 children (3.57%) were born to consanguineous parents (Fig.-1).

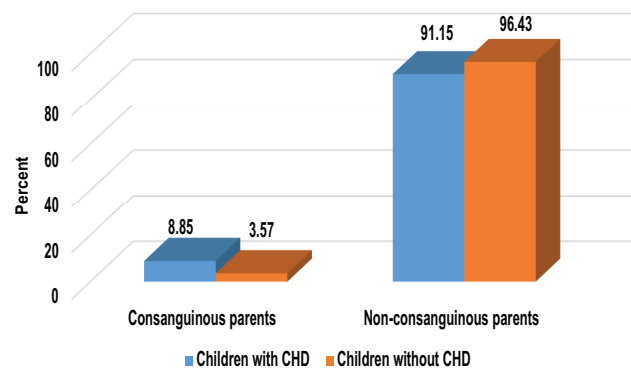


Fig.-1 Distribution of gender

Among children who had CHDs born to consanguineous parents, male were 56.52% and female were 43.48% in case group and in control group male were 60% and female were 40%. In case group 39.13% were from urban area and 60.87% were from rural area and in control group 30% were from urban area and 70% were from rural area. Most of the mother were in 21-30 years age group both in case (60.87%) and control (70%) group. Only 4.35% mother were more than 35 years of age in case and 20% in control. Most of the father of the respondents were in 30-35 years age group both in case (60.86%) and control (70%) [Table I].

Among children who had CHDs born to consanguineous parents, acyanotic congenital heart disease was present in 17(73.91%) cases of them ventricular septal defect in 34.79%, atrial septal defect in 17.39%, patent ductus arteriosus in 17.39% and pulmonary stenosis in 4.35% cases. Cyanotic congenital heart disease was present in 6(26.09%) cases of them transposition of great arteries in 8.69%, complex congenital heart disease in 8.69%, tetralogy of Fallot in 4.35% and pulmonary atresia in 4.35% cases (Table II).

Table I

Distribution of gender of children, residence and parental age at conception of consanguineous parents (n=33)

Gender, residence and parental age at conception		Case (n=23) Number (%)	Control (n=10) Number (%)
Gender of children	Male	13(56.52)	6(60)
	Female	10(43.48)	4(40)
Residence	Urban	9(39.13)	7(70)
	Rural	14(60.87)	3(30)
Maternal age in year	<20	1(4.35)	1(10)
	21-30	16(69.56)	7(70)
	30-35	5(21.74)	0(0)
	>35	1(4.35)	2(20)
Paternal age in year	<20	0(0)	0(0)
	21-30	7(30.35)	2(20)
	30-35	14(60.86)	7(70)
	>35	2(8.69)	1(10)

Table II

Type of CHD among children born to consanguineous parents (n=23)

Type of CHD	Number	Percent	
Acyanotic CHD	Ventricular septal defect	8	34.79
	Atrial septal defect	4	17.39
	Patent ductus arteriosus	4	17.39
	Pulmonary stenosis	1	4.35
Cyanotic CHD	Transposition of great arteries	2	8.69
	Complex congenital heart disease	2	8.69
	Tetralogy of Fallot	1	4.35
	Pulmonary atresia	1	4.35

In the case group, 23 children (8.85%) were born to consanguineous parents. In the control group, only 10 children (3.57%) were born to consanguineous parents. CHD was significantly higher among children born to consanguineous parents ($p < 0.05$) [Table III].

Table III
Association of consanguinity and CHD

Consanguinity	Case N=260	Control N=280	p value
Present	23	10	0.01
Absent	237	270	

Chi square test (χ^2) was done to find out level of significance

Risk factors on bivariate analysis were introduced into a logistic regression model as independent factors and dependent variable was CHDs. On logistic regression analysis consanguinity ($p = 0.02$) was independently associated with CHDs. Children who born to consanguineous parents had 2.5 times risk of developing CHDs compared to those who were not born to consanguineous parents (Table IV).

Table IV
Risk factors for developing CHDs using multivariate logistic regression

Risk factors	B	SE	p value	OR	95% CI for OR
Sex of children	-0.311	0.180	0.08	0.733	0.515-1.042
Consanguinity	0.903	0.395	0.02	2.467	1.138-5.347
Residence	-0.427	0.244	0.08	0.652	0.404-1.053
Maternal age	0.413	1.383	0.76	1.512	0.100-22.758
Paternal age	1.302	1.126	0.24	3.676	0.405-33.389

Discussion

Among study population consanguinity was present in 33(6.11%) cases. In the case group 23 children (8.85%) were born to consanguineous parents and in control group 10 children (3.57%) were born to consanguineous parents. CHDs were found significantly higher in children born to consanguineous parents ($p < 0.05$). An elevated OR was observed among children with CHDs who born to

consanguineous parents compared to those who were not born to consanguineous parents. Among consanguineous parents most of the mothers were in 21-30 years age group both in case (90.7%) and control (85%). Only 4.35% mothers age were more than 35 years in case and 20% in control. Most of the father of the respondents were in 30-35 years age group both in case (60.86%) and control (70%). Among children who had CHDs born to consanguineous parents, acyanotic congenital heart disease was present in 17(73.91%) cases of them ventricular septal defect in 34.79%, atrial septal defect in 17.39%, patent ductus arteriosus in 17.39% and pulmonary stenosis in 4.35% cases. Cyanotic congenital heart disease was present in 6(26.09%) cases of them transposition of great arteries in 8.69%, complex congenital heart disease in 8.69%, tetralogy of Fallot in 4.35% and pulmonary atresia in 4.35% cases

Danish cohort study by Oyen et al¹⁰ estimated recurrence risk ratios and found that among first-degree relatives, the recurrence risk ratio for the same defect was 8.15, whereas it was 2.68 for different heart defects. They have reported a 3.1% prevalence of CHD in first degree relatives. Fung et al⁸ in China found parental consanguinity in 3.5% of cases with CHD and was significantly associated with CHDs.

Becker et al¹¹ examined 1013 patients with CHDs and data indicate that the proportion of first-cousin matings among CHD patients is significantly higher than that of first-cousin intermarriages reported in the general population in the Saudi Arabia ($p < 0.001$). The study by El Mouzan et al¹² found that CHDs was present in 9.1 per 1000 consanguineous families versus 4.3 per 1000 non-consanguineous families ($p < 0.003$).

Nabulsi et al¹³ investigated the consanguinity profile of the 759 CHDs patients and observed that 20.2% of CHD patients were born to first cousins, whereas first cousin marriage in the control group was maximally 13.2%. The difference in cases and controls may suggest an association between CHDs and consanguinity ($p < 0.0001$).

In India, Dev et al¹⁴ in their hospital based cross sectional study analyzed 518 cases of CHDs. The parents of 2.92% of the control group were consanguineous versus 6.56% of the CHD families ($p < 0.005$). Ramegowda et al¹⁵ also found association between CHDs and consanguinity in India.

After controlling for confounders, Yunis et al¹⁶ reported first cousin consanguinity remained significantly associated with an increased risk of CHD: infants born to first cousin marriages had a 1.8 times higher risk of having a CHD diagnosed at birth compared to those born to unrelated parents ($p < 0.001$).

A relatively higher incidence of CHDs was observed in consanguineous marriages by various workers. Quite high incidence (>20%) was observed by Bassili et al¹⁷, Becker et al¹¹, Nabulsi et al¹³ and Ramegowda et al¹⁵. High incidence (10-20%) was observed by Yunis et al¹⁶. Almost similar incidence (<10%) to our study was observed by El Mouzan et al¹². Majority of studies are in support of a significant association between consanguineous parentage and presence of CHDs in their children.

Yunis et al¹⁶ found first cousin marriage was a significant risk factor for ventricular septal defect (VSD), atrial septal defect (ASD), hypoplastic left heart (HLH), and single ventricle (SV). No association was found with transposition of the great arteries, coarctation, pulmonary atresia (PA), atrioventricular septal defect (AVSD), and tetralogy of Fallot (TOF). Settin et al¹⁸ found the most common types of CHD in all population are ventricular septal defect, atrial septal defect, and tetralogy of Fallot. Fazeriandy et al¹⁹ showed that CHDs found in children from consanguineous parents were atrial septal defect (25%), persistent ductus arteriosus (24%), ventricular septal defect (30%), hypoplastic right ventricle (2%), and transposition of the great arteries (6%). This findings are similar to the present study. A study in United Arab Emirates found atrial septal defect (49%) as the most common type of CHD.²⁰ A South Indian study found that the most common CHDs were atrial septal defect and persistent ductus arteriosus.¹⁵ In contrast, a Pakistani study reported that ventricular septal defect (most common), persistent ductus arteriosus, atrial septal defect, pulmonary stenosis, tetralogy of Fallot, transposition of great arteries, and hypoplastic right ventricle were the common CHDs among consanguineous parents.²¹ Hoffman et al²² in their study in Iraq found that the most common CHD was non-cyanotic type, which was atrial septal defect (66.6%). Other cases were ventricular septal defect, persistent ductus arteriosus

and transposition of the great arteries. A similarity in our study was that acyanotic CHDs were more commonly found, with transposition of the great arteries as the most common cyanotic CHD.

This study have some limitations. First, to what extent could confounding play a role in differences between case and control groups? This study used controls from the same hospital to minimize potential confounders. Second, this study determined consanguinity considering at least first and second cousin unions. The history of consanguinity also relied largely on the report by the parent of a child with congenital heart disease. There may be possibility of reporting bias in eliciting the history of consanguinity. In this study association between subtypes of CHDs with consanguinity was also not performed.

Consanguinity should be considered in empiric risk estimates in genetic counselling.²³ Health care providers need to care for families involved in consanguineous unions and discuss and manage potential health concerns in an appropriate manner.

Conclusions

Parental consanguinity is significantly associated with CHDs.

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